Synthesis and Absolute Configuration of Enantiomerically Pure D3-Trishomocubanes (Pentacyclo[6.3.0.03,10.3,04,6]undecane) and Trishomocubanones

By Günter Helmchen and Gerhard Staiger

Rigid chiral hydrocarbons and ketones are of special interest as test cases for chiroptic theories. Outstanding representatives are the enantiomeric trishomocubanes (2f) and (3f), in that they are apparently the smallest stable organic molecules of the point symmetry group D3h.

While racemic trishomocubane is very readily accessible via rearrangement of the alcohols (1a) and (1b) to the stereoisomeric 4,7-diiodotrishomocubanes with hydriodic acid and their subsequent reduction with zinc, only relatively tedious methods exist for the synthesis of derivatives appearing suitable for separation of the enantiomers. We have found that 4-hydroxy-7-iodotrishomocubanes are formed in good yields as intermediates in the first mentioned reaction and that these can be easily resolved into their enantiomers. The structures and properties of the new compounds are summarized in Table 1.

Heating a mixture of the diols (1a) and (1b) with concentrated hydriodic acid at 70°C (15h) followed by chromatographic separation of the reaction products affords (2, 3a) and (2, 3b) in 54% and 13% yield, respectively. Assignment of configuration—confirmed in the case of (2, 3a) (vide infra)—was based on the fact that under the same conditions these compounds are also formed from the cyclic ether (1c) in a constant ratio of 6:5:1 independent of the reaction time and that (2, 3a) does not isomerize to (2, 3b).

Complete separation of the enantiomers (2a) and (3a) was achieved by liquid chromatography of their diastereomeric esters (2c) and (3c) with (−)-camphanic acid [silica gel columns, petroleum ether/ethylic acetate (92:8), separation factor: 1.1]. Pure (2c) can also be obtained in 30% yield by crystallization of the mixture from ethyl acetate. Like the (−)-camphanic acid, which was prepared from natural (+)-camphor, (2c) and (3c) and their secondary products described below were enantiomerically pure. Reduction of (2c) with zinc/glacial acetic acid and hydrolysis of the product with ethanolic potassium hydroxide solution yielded (−)-4-trishomocubanol (2d), which in turn furnished (−)-trishomocubanone (2e) by Jones-Kiliani oxidation (97% yield in each case). Wolff-Kishner reduction of (2e) afforded the readily volatile, camphor-like smelling (−)-trishomocubane (2f) in 80% yield. The compounds of the enantiomeric series were prepared analogously from (3c).

An extraordinarily reliable and simple 1H-NMR method recently developed by us was used for determination of the absolute configuration: (−)-(2a), obtained by hydrolysis of the ester (2c), was esterified with (S)-2-phenylbutyric chloride to give (2g). The 1H-NMR spectrum (CDCl3) of this compound shows a signal at δ = 3.88 ppm for H-7. The corresponding signal of the (R)-2-phenyl butyrate occurs at δ = 3.82 ppm, which was inferred from the spectrum of a mixture of the esters (2c) and (3c) with (−)-camphanic acid. From these data it follows that (−)-(2a) has the 3S,4R,7S configuration. This result was confirmed by an X-ray structure analysis of (2e) (cf. Fig. 1).

Table 1. Configuration and physical properties of trishomocubane derivatives (2) and (3).

| (a) | H | OH | H | 1 | 3S,4R,7S | 132 | 116 | −65.4° | (c = 2, ethanol) |
| (b) | H | OH | H | 1 | 3S,4R,7S | 162 | 138 | −21.8° | 20.4° | (c = 2, acetone) |
| (c) | H | OH | H | 1 | 3S,4R,7S | 166 | 147° | −147° | (c = 2, ethanol) |
| (d) | −O | H | H | 3S | 159 | −99.1° | (c = 2, c-hexane) |
| (e) | H | H | H | 3S | 149 | −164° | (c = 1.3, c-hexane) |
| (f) | H | OCOR5 | H | I | 3S,4R,7S |

[a] All the compounds have further chirality centers besides those specified; their configurations follow logically.
[b] Determined according to the Drude equation from measured values at 578 and 546 nm.
[c] R5−COOH = (−)-camphanic acid.
[d] R5−COOH = (+)-(S)-2-phenylbutyric acid.

Fig. 1. Molecular structure of the ester (2c).
Synthetic Hemopolymers for Reversible Binding of Molecular Oxygen

By Ernst Bayer and Gunter Holzbach[*]

Dedicated to Professor Hans-Joachim Bielig on his 65th birthday

Myoglobin and hemoglobin number among the most thoroughly studied biologically active proteins. Although the structure of these metalloproteins and their mode of action have been largely elucidated it has so far proved impossible to synthesize analogous heme complexes which reversibly bind oxygen under physiological conditions (20 to 40 °C; aqueous solution); such substance would play a very important role in the development of blood substitutes. Reversible oxygenation of model complexes containing heme has been observed only at low temperatures or in nonphysiological media[11]. Replacement of the protein component of an enzyme or an oxygen carrier appears to be difficult, even in well investigated biopolymers. Since protein synthesis is still too complicated or unreliable by presently available methods, and proteins are too unstable for practical use in catalyst systems, attention should be directed to synthetic polymers functionalized in suitable manner.

We have now synthesized heme-containing functionalized polymers for the reversible transport of oxygen which share the following properties with the natural oxygen carriers hemoglobin and myoglobin:
1) good solubility in water in order to achieve high concentrations of O2;
2) hindrance of irreversible oxidation of the oxygen complex by the functionalized polymer;
3) imitation of the distal imidazole.

Polyvinylpyrrolidinone, poly[ethylene glycol bis(glycine ester)][22], (1), and polyurethanes of structure (2) from polyethylene glycols (PEG) and diisocyanates[2b] were used as the basic polymers. Di-tert-butylxycarbonylhistidine[3] is coupled to the free amino groups of polymers (1) and (2) in compliance with the procedures of liquid phase peptide synthesis with dicyclohexylcarbodiimide (DCCI)[4]. The amino protecting group of the histidine is then removed with trifluoroacetic acid/CH3Cl (1:1) and the amino group coupled with DCCI to a carboxy group of hemin. The hemin content of poly[ethylene glycol bis(glycylhistidylhemin)] (3) is 73%, that of the histidylhemin derivative of the polymeric urethane (4) 100%, based on the amino groups of the starting polymer (1) and (2), respectively.

In the two functionalized polymers (3) and (4), histidine is linked with the carboxy group of a propionic acid residue of heme to form the amide. This arrangement prevents optimum coordinative fixation of the imidazolyl nitrogen of the histidine residue to the iron of heme for steric reasons. The histidine bound in this way can therefore be compared with the distal histidine in myoglobin. The only other requirement for synthesis of an oxygen carrier is an imidazole ligand corresponding to the proximal histidine of natural oxygen carriers. This approach was adopted in the case of polymer (4) by addition and coordinative bonding of imidazole or imidazole derivatives. It is better however, to introduce an additional covalent bond between the proximal imidazole and the polymer. In the case of (3), 3-[imidazolyl]propylamine[5] was therefore coupled to the second propionic acid group—once again using the methods of liquid phase peptide synthesis with DCCI/hydroxybenzotriazole. In the polymeric product (5) this imidazole group can undergo optimal coordination with the iron.

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